

REMARKS

The Official Action of February 5, 2007, and the prior art relied upon therein have been carefully reviewed. The claims in the application are now only claims 1-6, and these claims define patentable subject matter warranting their allowance. Accordingly, the applicants respectfully request favorable reconsideration and allowance.

Acknowledgement by the PTO of the receipt of applicants' papers filed under §119 is noted.

The disclosure has been amended by incorporating the heading "Brief description of Drawings" as required by the Examiner.

Claims 7 to 19 have been cancelled so that rejection of claims 13 to 19 under 35 U.S.C. 101 no longer applies.

Claims 2 and 3 as amended no longer recite that R⁵ and R⁶ or R⁷, R⁹ are a carbohydrate, a steroid, a triterpene and alkaloid, a lignane, or generally "compounds of pharmacological interest", but only that R⁵ and R⁶ and R⁷, R⁹ =H or a functionalized carbon chain bearing an amine, amino acid, aminoester function. Therefore, the rejection of these claims 2 and 3 under 35 U.S.C. 112 (first paragraph) is obviated.

Claims 10 and 11 have been cancelled so that the Examiner's rejection of these claims no longer applies.

In order to overcome the Examiner's rejection of claims 1 to 4 under 35 U.S.C. 112 the notations (...) and the recitation "i.e." have been cancelled.

The Examiner's objection concerning the fact that claim 2 is not coherent with claim 1 no longer exists due to the amendment made in claim 1.

As can be seen, in the amended claim 1

R^1 is defined as a group comprising a functionalized carbon chain bearing at least a function selected from the group consisting of an amine, amide or acid function,

R^2 is a free alcohol function OH or a protected alcohol function using a protective group GP as defined in the specification text.

The hydrogen in the definition of Y, Y', Y" has been cancelled.

The objections and the rejections under §112 are thus all believed to be fully addressed with the amendments made above. Withdrawal of such objections and rejections is respectfully requested.

Claims 1 and 3 have been rejected under §102 as anticipated by what the examiner has identified as Quirion et al (Tetrahedron letters, 2001), but this publication is in the name of Marcotte et al, Quirion¹ being the sixth listed author of the publication. Applicants will refer to this publication as "Marcotte". Claims 1 and 3 are alternatively rejected under §103 as obvious from Marcotte in view of Wong et al 1998 (Wong). These rejections are respectfully traversed.

The compounds as claimed in the amended claim 1 (and claim 3 which depends therefrom) as well as in the amended claim 4 are not disclosed or suggested by Marcotte, which concerns the synthesis of new α - and β -gem-difluoromethylene C-glycosides in the galactose and glucose series.

Marcotte states (page 5879) that "using a difluoromethylene group in place of the anomeric oxygen bond is becoming a promising avenue for the preparation of a new glycoconjugate derivatives.... However a general synthesis of gem-difluoromethylene C-glycosides applicable to the most often encountered carbohydrates is still to [be] discover[ed] In a first attempt, we considered the nucleophilic attack of the ethylbromodifluoroacetate zinc reagent on an oxonium but all our attempts failed whatever the conditions. Disappointed by the absence of stereoselectivity, we then

¹ The present applicants comprise the same team as the authors of the Marcotte publication.

performed the cyclization using an intramolecular oxymercuration."

Then, the last paragraph of this document (page 5881) states that:

Currently experiments are underway to prepare compound 1. Our works deals with functional transformation of the carboxylic ester to obtain the desired amino acids. We are also studying new methods of cyclization to avoid the use of mercury salts (which cannot be used for medicine) and the application of this strategy to other biologically interesting carbohydrates.

It is clear that the applicants' claimed solution was found by the same team only one year later. The making of compound 1 was not enabled by Marcotte. The Marcotte publication neither anticipate nor makes obvious applicants' claims

It clearly appears that a gem-difluorinated compound having the formula of applicants' amended claim 1, as well as the preparation method thereof (claim 4), was not discovered at the time the article was prepared for publication and certainly is not disclosed in the publication. This document only states that a synthesis of gem-difluoromethylene C-glycopyranosides was achieved via a Reformatsky reaction on an aldehyde and subsequent intramolecular cyclisation involving either the opening of an epoxide or an oxymercuration.

In addition the fact should be emphasized that transformation of HgBr into OH used in Marcotte is not

applicable to medicinal compounds (presence of Hg) and never leads to the right stereoisomer.

For this reason applicants most strongly believe and submit that the invention as claimed in claims 1 and 4 complies with the novelty and inventiveness requirements with respect to Marcotte et al, Tetrahedron Letters 2001.

Withdrawal of the rejection under §102 based on Marcotte is in order and is respectfully requested.

The rejection under §103 based on Marcotte in view of Wong is also respectfully traversed, the commentary made immediately above concerning Marcotte being respectfully repeated by reference.

As stated by the Examiner, Wong teaches a sugar derivative that is structurally similar in certain respects to the compound as instantly claimed. However, Wong does not teach a derivative comprising a gem-difluoromethylene as in the claimed compounds.

As specified in the preamble of the specification text, the claimed glycoconjugated compounds formed by conjugation between a sugar and another compound (aglycone) are fragile relative to several enzymatic systems including protease enzymes and hydrolase enzymes due to the presence of an oxidic bond (a bond involving oxygen said to be in an anomeric position).

In order to overcome this drawback, the present invention proposes to replace the oxygen atom of the oxidic bond with a difluoromethylene group in order to provide increased stability to glycoconjugated compounds in a biological medium. This O/CF₂ transposition is suitable for miming oxygen on the electronic level, both fluorine atoms playing the role of both free doublets of oxygen.

It clearly appears that Wong does not suggest this solution.

In addition, in comparison with Wong's solution, the applicants' solution involves a replacement of the methylene group of the Wong's compositions by difluoromethylene, more adapted for miming oxygen present on the S1e^x, which permits an increase in the activity of the obtained product. The position of the peptidic chain in β (rather than in α as in the Wong component) and the anomeric alcohol in α does not change the properties of the resulting molecules with respect to selection.

The applicants' solution cannot obviously result from the teaching of Wong and of Marcotte together due to the fact that at the time of the present invention Marcotte only disclosed a synthesis of gem-difluoromethylene C-glycosides by a cyclization using an intramolecular oxymercuration ("A diastereoselection using formation via an intramolecular

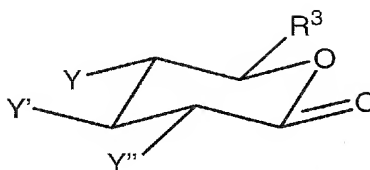
oxymercuration was the key step"). However such a solution is prohibited for medical purposes. For this reason, Marcotte et al state on page 5881 of the article that they are studying a new method of cyclization to avoid the use of mercury salts. This solution to these problems was solved only more than one year later. For these reasons the teaching of Marcotte et al cannot be obviously combined with Wong.

In short, applicants submit that it would not have been obvious to even attempt to combine the references; and, even if one attempted to combine the references, the resultant combination would not reach the claimed subject matter because of the aforementioned deficiencies in the prior art as set forth above.

Withdrawal of the rejection based on §103 is in order and is respectfully requested.

Claims 4-9 have been rejected as obvious under §103 from Lerner et al 1979 (Lerner) in combination with Furstner 1989 (Furstner). This rejection is respectfully traversed.

Even if such combination were obvious, respectfully not admitted by applicants, such combination still would not reach the claimed subject matter, i.e. would not teach a reaction, in the presence of zinc at reflux of THF acting as solvent or in the presence of a lanthanide derivative, between a lactone of formula



and a halogenated derivative of general formula $\text{XCF}_2\text{CO}_2\text{R}^8$, wherein X is a halogen and R^8 is an alkyl so as to obtain an ester function which can be either reduced to alcohol then oxidized into an aldehyde or hemi-acetal, or directly reduced into aldehyde.

Therefore claim 4 defines patentable subject matter, and should be allowed.

Claims 5 and 6 depends from and incorporate the subject matter of claim 4, and are therefore patentable for the same reasons as claim 4.

Claims 7-9 are no longer pending, and so the rejection need not be addressed with respect to those claims.

Claim 11 has been rejected as obvious under §103 from Ullas et al 2002. Claim 11 is no longer pending, and so applicants need not address this rejection at the present time.

In view of the foregoing, early and favourable reconsideration of this office action together with the allowance of the amended claims 1 to 7 is respectfully solicited.

The prior art documents of record and not relied upon by the PTO have been noted, along with the implication that such documents are deemed by the PTO to be insufficiently material to warrant their application against any of applicants' claims.

Applicants believe that all issues raised in the Official Action have been addressed above in a manner that should lead to patentability of the present application. Favorable consideration and early formal allowance are respectfully requested.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By



Sheridan Neimark
Registration No. 20,520

SN:kg
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
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